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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/242,343	04/12/99	VOLLENBROICH	D 2694-119P

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/242,343	Vollenbroich et al.
Examiner	**Art Unit**
Brenda Brumback	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 3, 2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11, 13-15, 18, and 19* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-11, 13-15, 18, and 19* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The request filed on 04/26/2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/242,343 is acceptable and a CPA has been established. An action on the CPA follows.

2. This action is responsive to the amendments filed 02/26/2001 and 05/03/2001. Claims 1, 10, and 15 were amended. New claims 18 and 19 were added. Claims 12, 16, and 17 were canceled. Claims 1-11, 13-15, 18, and 19 are pending and under examination.

Please note: for clarification of the record, claims 12 and 17 were canceled with the amendment filed 02/26/2001, which was entered as per the request filed with the CPA on 04/26/2001.

Claim Rejections - 35 USC § 112

3. The rejection of claims 1-10 and 13-16 under 35 U.S.C. 112, first paragraph, as not enabled for inactivating viruses in cell cultures using concentrations grater than 70μM is withdrawn pursuant to applicant's amendment thereof.

4. The rejection of claim 1 as indefinite for reciting cell cultures and biological products is withdrawn pursuant to applicant's amendment thereof.

The rejection of claim 10 under 35 U.S.C. 112, as indefinite for recitation of immunodeficiency viruses is withdrawn pursuant to applicant's amendment thereof to recite specific immunodeficiency viruses and arguments, which were persuasive. Herpes viruses are understood to mean any of the family *Herpesviridae*, as per applicant's arguments and Exhibit A.

The rejection of claim 12 for insufficient antecedent basis is now moot, as claim 12 has been canceled.

Claim Rejections - 35 USC § 103

5. The Advisory Action mailed 03/15/2001 indicated that applicant's proposed claim amendments would overcome the rejection of claims 1, 3-7, 9, and 10 as unpatentable over Itokawa et al. and the rejection of claims 2 and 13 under 35 U.S.C. 103(a) as being unpatentable over Itokawa et al. in view of Horowitz et al. However, upon further consideration, this rejection is maintained. Claims 14, 15, 18, and 19 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Itokawa et al. for the reasons of record. Applicant's arguments filed 02/26/2001 and reiterated in the amendment filed 05/03/2001 have been fully considered but they are not persuasive for the following reasons.

Applicant argues that the present claims have been amended to recite that the degree of viral inactivation achieved using the claimed method is an inactivation factor of $>10^4$, whereas Itokawa et al. disclose only a moderate amount of anti-HIV-1 activity with no disclosure of an inactivation factor of $>10^4$. Absent some evidence to the contrary, applicant's claimed method of

inactivation of $>10^4$ viruses by contacting the viruses with the cyclic lipopeptide agent at a selected concentration of 1-100 μM would seem to constitute routine optimization of a known test method, because Itokawa et al. teach contacting the virus with the agent.

Applicant further argues that there is no suggestion in Itokawa et al. that one would be able to achieve the degree of activation in the short time recited in the present invention based on the teaching of moderate virus inactivation, and that for this reason, the rejection is based on hindsight reasoning. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the present case, the teaching of viral inactivation at moderate levels would have pointed directly to its use for inactivating viruses. Applicant is reminded that absolute predictability is not required, but rather a reasonable expectation of success. The teachings found in Itokawa et al. support such a reasonable expectation of success.

Applicant also argues that "At the time of Itokawa et al., thousands of compounds had been identified which had 'moderate' viral inactivation activity..."; however, applicant has provided no evidence in support of this argument. Argument in the absence of evidence is not persuasive.

6. The rejection of claims 1, 3, 9, and 10 under 35 U.S.C. 103(a) as being unpatentable over Naruse et al. is maintained. Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that Naruse et al. disclose a method of indirect viral inactivation because with the method of Naruse et al., the replication of the viral nucleic acid in the host cell is being targeted and affected, with viral growth and multiplication inhibited, whereas the claimed invention is directed to a method of direct viral inactivation. Firstly, applicant's assertion that Naruse et al. is teaching inhibition of viral replication rather than virus inactivation is purely conjectural at best. Naruse states that "Pumilacidin exhibited antiviral activity against HSV-1-KOS strain ..." (page 267, first paragraph). Naruse is silent as to the exact means whereby Pumilacidin inactivates viruses. Secondly, even if Naruse had taught inhibition rather than inactivation, applicant's arguments regarding "direct" inactivation versus "indirect" viral inhibition are really claiming a new property of a previously known product. The claiming of a new property for a previously known product does not impart patentability. Lastly, applicant's argument that the measurement of viral growth and multiplication indicates inhibition, and not inactivation, is not persuasive because the art recognized method for measuring viral inactivation is to test for viral infectivity in susceptible cell cultures, regardless of the mode of action of the inactivating or inhibitory agent. In fact, this is the same method used in applicant's disclosure to measure viral inactivation (see page 29).

7. The rejection of claims 2 and 14 under 35 U.S.C. 103(a) as being unpatentable over either Itokawa et al. or Naruse et al. in view of Horowitz et al. and the rejection of claims 8 and 11 under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Itokawa and Naruse in view of Vater et al. are maintained for the reasons of record. No additional arguments regarding these rejections were set forth in applicant's response.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

8. Claims 1-9, 13-15, 18, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites an inactivation factor $>10^4$. The claim is indefinite for failing to recite the unit of measurement denoted by the numerical value. Without recitation of the unit of measurement the metes and bounds of the claimed invention cannot be determined and the claim is indefinite.

Applicant's arguments regarding this rejection have been fully considered but they are not persuasive for the following reasons. Applicant argues that the recited dimensions are "unit-less" because this factor is a ratio which was calculated as the ratio of the virus titer in the absence of an inactivation agent of the invention as control and the virus titer of the agent treated sample. While the disclosure may teach measuring virus titers in the presence and absence of the

inactivation agent and calculation of the difference, the numerical value recited in the claim is not that of a ratio, as is recognized in the art. Webster's II New Riverside Dictionary (page 976, attached hereto) defines a ratio as the relation in number of degree between two similar things and teaches that a ratio is written as two numbers separated by a colon or a slash (*i.e.* 7:4 or 7/4). The value recited in the claim is a single value denoting the difference in viral titers in the absence and presence of an inactivating agent. The disclosure teaches the unit of measurement as the number of infectious doses or ID_{50}/ml (see page 17, line 6, for example). This rejection may be overcome by amending the claim to add "ID_{50}/ml" after the numerical value.

Claim 2 is indefinite for recitation of "temperatures higher than room temperature", because the metes and bounds of the claimed range cannot be determined. The disclosure fails to teach what temperatures are encompassed within "room" temperature. Furthermore, the claimed range lacks an upper limit. Absent a well-defined lower limit and an upper limit, the metes and bounds of the claimed range cannot be determined and the claim is indefinite.

Claim 18 recites biological products selected from the group consisting of blood products, products isolated from blood, and biotechnological pharmaceutical products consisting of human proteins. The claim is indefinite because the distinction between "blood products" and "products isolated from blood" is unclear. Furthermore, claim 18 recites the broad recitation "biotechnological pharmaceutical products" and also recites "blood products" and "products isolated from blood" which are narrower statements of the range/limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation

(in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Claim 19 is indefinite as being in improper Markush format (see Ex parte Markush, 1925 C.D. 126 and In re Weber, 198 USPQ 334). A Markush group must set forth a plurality of members belonging to a recognized physical or chemical class or to an art-recognized class (MPEP 2173.05(h)). In the instant case, the claim recites a single species in Markush format. Correction is required.

9. Claims 1-10, 13-15, 18, and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inactivation of lipid-enveloped viruses in biological products intended for *in vitro* use, does not reasonably provide enablement for inactivation of lipid-enveloped viruses in pharmaceutical and blood products intended for *in vivo* administration.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the

presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a method of inactivating lipid-enveloped viruses in biological products comprising contacting a cyclic lipopeptide with the product at room temperature or higher for 30 minutes to 2 hours. The claimed biological products encompass blood products, products containing blood cells, vaccines, and other pharmaceutical products for *in vivo* administration.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that the presence of proteins and cellular material in biological products is problematic in achieving effective viral inactivation. The art further teaches that for an inactivating agent to be effective, it must be able to inactivate extracellular viruses in the presence of proteins, entrapped or cell-bound virus, and intracellular virus (see Wagner et al., Transfusion Medicine Reviews, vol. V, No. 1:18-32, 1991, page 19, second full paragraph, and page 24, column 2, first full paragraph). The art teaches that agents which are effective in inactivating viruses may be unacceptable for treating blood products intended for *in vivo* administration due to toxicity, damaging effects upon blood cells, and/ or mutagenesis (see Wagner et al., page 23, fist sentence of the first full paragraph; page 25, column 1, first full paragraph, and column 2, first full paragraph, through page 26, line 2; page 28, the paragraph bridging columns 1 and 2, and the paragraph bridging pages 28 and 29).

The amount of direction or guidance present and the presence or absence of working examples: Given the teachings of unpredictability found in the art, detailed teachings are required to be present in the disclosure addressing the issues of effectiveness in biological products containing both cells and high concentrations of proteins and the absence of toxicity, deleterious effects upon cellular material, and mutagenesis. The disclosure teaches how to prepare the claimed surfactins (Examples 1-4, pages 9-16) and teaches viral inactivation in cell culture medium, bovine serum albumin, and a cell culture (Examples 5-8, pages 17-23; Example 10, pages 2526; and Examples 11 and 12, pages 27-30). The disclosure teaches that surfactin concentrations are not cytotoxic to cells in culture at levels below about 40μM, with some variation depending on the cell line tested (Examples 9 and 10, pages 23-26). However, the disclosure does not address inactivation of cell-bound or intracellular viruses in the presence of high concentration of proteins (as would be the case in whole blood) and does not address the potential for inactivation of sensitive blood cells, such as platelets, which the art teaches are more sensitive to changes in the external environment than are other cells (see Wagner et al., page 28, the paragraph bridging columns 1 and 2). The disclosure is completely silent as to potential toxic or mutagenic side-effects resulting form *in vivo* administration of the treated product.

The breadth of the claims and the quantity of experimentation needed: Given the teachings of unpredictability regarding effectiveness of an antiviral agent in inactivating cell-bound and intracellular viruses in the presence of concentrated proteins, potential deleterious effects upon the product, and undesirable side effects resulting from *in vivo* administration of the treated

product, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback
May 31, 2001

Brenda Brumback
BRENDA BRUMBACK
PATENT EXAMINER